CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074602

Trade Name : LACTULOSE SOLUTION 10g/15ml

Generic Name: Lactulose Solution 10g/15ml

Sponsor : Morton Grove Pharmaceuticals, Inc.

Approval Date: November 14, 1996

DW

ANDA 74-602

NOV 14 1996

Morton Grove Pharmaceuticals, Inc.
Attention: William F. Hendershot, Ph.D.
Agent for: Morton Grove Acquisitions Corp.
6451 West Main Street
Morton Grove, IL 60053

Dear Sir:

This is in reference to your abbreviated new drug application dated December 30, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Lactulose Solution USP, 10 g/15 mL.

Reference is also made to your amendments dated September 12, 1995 and July 2, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Lactulose Solution USP, 10 g/15 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Chronulac® of Hoechst Marion Roussel.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-602 LACTULOSE SOLUTION, USP 10 g/15 mL
PRODUCT CODE 8037
1 QUART (946 mL) FINAL PRINTED CONTAINER LABELING

Each 15 mL (tablespoonful) contains:
10 g lactulose (less than 1.6 g galactose, less than 1.2 g lactose and 0.1 g or less of fructose).

3 60432-037-32 7

MGP

NDC 60432-037-32

LACTULOSE SOLUTION, USP 10 g/15 mL

INDICATIONS AND DOSAGE:
FOR THE TREATMENT OF CONSTIPATION. SEE INSERT LABELING FOR FULL INFORMATION.

DO NOT USE IF BAND PRINTED "SEALED FOR YOUR PROTECTION" AROUND CAP IS BROKEN OR MISSING.

BULK CONTAINER — NOT FOR HOUSEHOLD USE

CAUTION: Federal law prohibits dispensing without prescription.

NET: 1 Quart (946 mL)

USUAL ADULT DOSAGE: 15 to 30 mL (1 to 2 tablespoonfuls) daily. See accompanying package insert.
Since lactulose does not exert its effects until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce a normal bowel movement.
Some patients have found that lactulose may be more acceptable when mixed with fruit juice, water or milk.
WARNING: **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.** In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.
Store at controlled room temperature, 15 °-30 °C (59 °-86 °F).
Do Not Freeze
KEEP TIGHTLY CLOSED
Product may darken slightly but the therapeutic action is not affected. Do not use if extreme darkening or turbidity occurs.
See accompanying information.
Dispense in original container or in a tight, light-resistant container as defined in the USP, with a child-resistant closure.
To The Pharmacist: When ordering this product, include the product number (or NDC) in the description.
Packaged By: Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053
Manufactured By: Morinaga Milk Industry Co., Ltd.
Tokyo 108, Japan

50-8037-32
ISS. 2-96

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ANDA 74-602 LACTULOSE SOLUTION, USP 10 g/15 mL
PRODUCT CODE 8037
8 FL OZ (237 mL) FINAL PRINTED CONTAINER LABELING

DO NOT USE IF BAND PRINTED "SEALED FOR YOUR PROTECTION" AROUND CAP IS BROKEN OR MISSING.

Each 15 mL (tablespoonful) contains: 10 g lactulose (less than 1.6 g galactose, less than 1.2 g lactose and 0.1 g or less of fructose).

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NDC 60432-037-08

LACTULOSE SOLUTION, USP 10 g/15 mL

INDICATIONS AND DOSAGE:
FOR THE TREATMENT OF CONSTIPATION. SEE INSERT LABELING FOR FULL INFORMATION.

CAUTION: Federal law prohibits dispensing without prescription.

NET: 8 fl oz (237 mL)

USUAL ADULT DOSAGE: 15 to 30 mL (1 to 2 tablespoonfuls) daily. See accompanying package insert.
Since lactulose does not exert its effects until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce a normal bowel movement.
Some patients have found that lactulose may be more acceptable when mixed with fruit juice, water or milk.
WARNINGS: **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.** In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Do Not Freeze
KEEP TIGHTLY CLOSED
Product may darken slightly but the therapeutic action is not affected. Do not use if extreme darkening or precipitate occurs. See accompanying information.
Dispense in original container or in a tight, light-resistant container as defined in the USP, with a child-resistant closure.
To The Pharmacist: When ordering this product, include the product number (or NDC) in the description.
Packaged By: Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053
Manufactured By: Morinaga Milk Industry Co., Ltd.
Tokyo 108, Japan

50-8037-08
ISS. 2-96

MGP

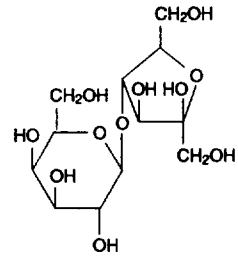
LACTULOSE SOLUTION, USP
10 g/15 mL

DESCRIPTION

Lactulose solution is a synthetic disaccharide in solution form for oral administration. **Each 15 mL of lactulose contains:** 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose and 0.1 g or less of fructose).

Lactulose solution is a colonic acidifer which promotes laxation.

The chemical name for lactulose is 4-O-β-D-galactopyranosyl-D-fructofuranose. It has the following structural formula:



$C_{12}H_{22}O_{11}$
The molecular weight is 342.30. It is freely soluble in water.

CLINICAL PHARMACOLOGY

Lactulose is poorly absorbed from the gastrointestinal tract and no enzyme capable of hydrolysis of this disaccharide is present in human gastrointestinal tissue. As a result, oral doses of lactulose reach the colon virtually unchanged. In the colon, lactulose is broken down primarily to lactic acid, and also into small amounts of formic and acetic acids by action of colonic bacteria, which results in an increase of osmotic pressure and slight acidification of the colonic contents. This in turn causes an increase of stool water content and softens the stool.

Since lactulose does not exert its effect until it reaches the colon, and since transmit time through the colon may be slow, 24 to 48 hours may be required to produce the desired bowel movement.

Lactulose given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

INDICATIONS AND USAGE

For the treatment of constipation. In patients with a history of chronic constipation, lactulose solution therapy increases the number of bowel movements per day and the number of days on which bowel movements occur.

CONTRAINDICATIONS

Since lactulose solution contains galactose (less than 1.6 g/15 mL), it is contraindicated in patients who require a low galactose diet.

WARNINGS

A theoretical hazard may exist for patients being treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H_2 gas in significant concentration in the presence of an electrical spark may result in an explosive reaction. Although this complication has not been reported with lactuloee, patients on lactulose therapy undergoing such procedures should have a thorough bowel cleansing with a non-fermentable solution. Insufflation of CO_2 as an additional safeguard may be pursued but is considered to be a redundant measure.

PRECAUTIONS

General: Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetics.

Information for Patients: In the event that an unusual diarrheal condition occurs, contact your physician.

Laboratory Tests: Elderly, debilitated patients who receive lactulose for more than six months should have serum electrolytes (potassium, chloride, carbon dioxide) measured periodically.

Drug Interactions: Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with lactulose solution.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility.

There are no known animal data on long-term potential for mutagenicity.

Administration of lactulose solution in the diet of mice for 18 months in concentrations of 3 and 10 percent (w/w) did not produce any evidence of carcinogenicity.

In studies in mice, rats, and rabbits doses of lactulose solution up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

Pregnancy

Teratogenic Effects — Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to 3 to 6 times the usual human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to lactulose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lactulose solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Precise frequency data are not available.

Initial dosing may produce flatulence and intestinal cramps, which are usually transient. Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and hypernatremia.

Nausea and vomiting have been reported.

OVERDOSAGE

Signs and Symptoms: There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medications should be terminated.

Oral LD_{50}: The acute oral LD_{50} of the drug is 48.8 mL/kg in mice and greater than 30 mL/kg in rats.

Dialysis: Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

DOSAGE AND ADMINISTRATION

The usual dose is 15 to 30 mL (1 to 2 tablespoonfuls, containing 10 g to 20 g of lactulose) daily. The dose may be increased to 60 mL daily if necessary. Twenty-four (24) to 48 hours may be required to produce a normal bowel movement.

NOTE: Some patients have found that lactulose solution may be more acceptable when mixed with fruit juice, water or milk.

HOW SUPPLIED

Lactulose Solution, USP is a colorless to yellow, unflavored solution available in the following container sizes:
8 fl oz (237 mL) bottles
1 Quart (946 mL) bottles

Store at controlled room temperature, 15 °-30 °C (59 °-86 °F).

Do Not Freeze

Under recommended storage conditions, a normal darkening of color may occur. Such darkening is characteristic of sugar solutions and does not affect therapeutic action. Prolonged exposure to temperatures above 30 °C (86 °F) or to direct light may cause extreme darkening and turbidity which may be pharmaceutically objectionable. If condition develops do not use.

Prolonged exposure to freezing temperatures may cause change to a semisolid, too viscous to pour. Viscosity will return to normal upon warming to room temperature.

Dispense in original container or in a tight, light-resistant container as defined in the USP, with a child-resistant closure.

To The Pharmacist: When ordering this product, include the product number (or NDC) in the description.

CAUTION: Federal law prohibits dispensing without prescription.

Product No.: 8037

Packaged By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

Manufactured By:
Morinaga Milk Industry Co., Ltd.
Tokyo 108, Japan

28037 ISS. 6-96

DW

1. CHEMIST'S REVIEW NO.4

2. ANDA # 74-602

3. NAME AND ADDRESS OF APPLICANT
Morton Grove Pharmaceuticals
6451 West Main Street
Morton Grove, Illinois 60053

4. BASIS FOR SUBMISSION
Page 000011 includes a statement claiming that the patent has expired (Paragraph II certification). The following page states also that exclusivity has expired.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
Chronulac

7. NONPROPRIETARY NAME
Lactulose Solution

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission	December 30, 1994
Refuse to File Letter	February 2, 1995
Amendment	February 7, 1995
Acknowledgement	March 3, 1995
FDA Deficiency letter	June 1, 1995
Amendment	August 7, 1995
FDA Deficiency Letter	January 19, 1996
Amendment	February 23, 1996
FDA Deficiency Letter	June 4, 1996
Amendment	July 2, 1996

10. PHARMACOLOGICAL CATEGORY
Laxative

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

Comment:

*The firm was advised that all DMF references should be included on the 356h form filed with each new amendment. A new form should be submitted. The firm resubmitted this information on a new 356h.

13. DOSAGE FORM
Oral Solution

14. POTENCY
10 g/15 mL

15. CHEMICAL NAME AND STRUCTURE
4-O-beta-D-Galactopyranosyl-D-fructofuranose

16. RECORDS AND REPORTS
N/A

17. COMMENTS
All minor deficiencies have been resolved.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is now approvable.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.

DATE COMPLETED:
10/17/96

DIV

ANDA 74-602
74-603

FEB - 9 1996

Morton Grove Acquisition Corp.
Attention: William F. Hendershot, Ph.D.
6451 West Main Street
Morton Grove IL 60053

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Lactulose Solution USP, 10g/15 mL.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 5 1996

Lactulose Solution, USP	Morton Grove Pharmaceuticals
10 g/15 mL	Morton Grove, IL
ANDA #74-602	Submission Date:
ANDA #74-603	
Reviewer: Moo Park	August 30, 1995
Filename: 74602AW.895	September 12, 1995

Review of two Amendments

I. Objective

Review of Morton Grove's amendments to its waiver requests for its Lactulose Solution, USP, 10 g/15 mL, in ANDAs #74-602 and 74-603. The reference products are Marion Merrell Dow's Chronulac^R (Lactulose Solution), 10 g/15 mL (oral administration, ANDA #74602), and Cephulac^R (Lactulose) Syrup, 10 g/15 mL (oral or rectal administration, ANDA #74-603).

II. Comments

1. The test and reference products are a solution dosage form for oral or rectal administration. Morton Grove's formulations for the ANDAs #74-602 and 74-603 are exactly same.

Test and Reference Formulations
Amount/15 mL

Ingredient	Test Product	Reference Product (Chronulac^R and Cephulac^R)
Lactulose	10 g	10 g
Galactose		
Lactose		
Fructose		
Water	qs to 15 mL	qs to 15 mL

2. Drug Master File for the active ingredient, was reviewed by Dr. Karen Bernard as satisfactory as of 10/26/95.

3. Morton Grove's waiver requests are granted for ANDAs #74-602 and 74-603.

III. Recommendation

The Division of Bioequivalence agrees that the information submitted by Morton Grove Pharmaceuticals demonstrate that Lactulose Solution, USP, 10 g/15 mL, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waivers of *in vivo* bioequivalence study requirements for the test products for ANDAs #74-602 and 74-603 are granted. The Division of Bioequivalence deems Morton Grove's Lactulose Solution, USP, 10 g/15 mL, to be bioequivalent to Maion Merrell Dow's Chronulac® and Cephulac®, 10 g/15 mL.

The firm should be informed of the recommendation.

Moo Park

Moo Park, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

Ramakant M. Mhatre, Ph.D.
Branch Chief, Review Branch III
Division of Bioequivalence

Concur: See Memo

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

Date: _____

cc: ANDA #74-602 and 74-603 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Park), Drug File, Division File

File History: Draft (1/30/96); Final (2/1/96)